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1/77

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The Patent Office

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Gwent NP9 1RH

1. Your Reference — **AP/PB60212P**

19APR03 E801248-1 001030
P01/7700 0.00-0308968.7

2. Patent application number
(The Patent office will fill in this part) — **0308968.7**

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

GLAXO GROUP LIMITED
GLAXO WELLCOME HOUSE
BERKELEY AVENUE
GREENFORD
MIDDLESEX
UB6 ONN
GB

00473587003
Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its corporation — **GB**

4 Title of the invention — **MEDICAMENTS**

5 Name of your agent *(if you know one)* — **PETER I DOLTON**

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

GLAXOSMITHKLINE
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Patents ADP number *(if you know it)*

08321846001

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Country	Priority application number *(if you know it)*	Date of Filing (day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing (day / month / year)

8. Is a statement of inventorship and of right to grant a patent required in support of this request? *(Answer yes if:*
a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.

YES

See note (d))

Patents Form 1/77

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Continuation sheets of this form	-
Description	18
Claim(s)	1
Abstract	1
Drawing(s)	-

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Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patent Form 9/77)*	
Request for substantive examination *(Patent Form 10/77)*	
Any other documents *(please specify)*	

11. P. I. Donon

I/We request the grant of a patent on the basis of this application

Signature PETER I DONON 17April 2003
AGENT FOR THE APPLICANTS

12. Name and daytime telephone number of person to contact in the United Kingdom

JEAN HARNEY

020 8047 4420

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PB60212P

MEDICAMENTS

The present invention relates to therapeutic combinations comprising paroxetine and a Nk1 receptor antagonist, to pharmaceutical compositions containing said combinations and their use in the treatment of depression and /or anxiety.

Paroxetine ((-) trans-4-(4'-fluorophenyl)3-(3'-4'-methylenedioxyphenoxymethyl) piperidine) and its salts are commercially available and approved for use in humans for treatment and prophylaxis of, *inter alia,* anxiety, depression, obsessive compulsive disorder (OCD) and panic.

NK_1 receptor antagonists are known to be useful in the treatment of anxiety and depression, chemotherapy-induced nausea and vomiting and post-operative nausea and vomiting. Preclinical data suggest that NK_1 receptor antagonists may be useful in a variety of other disorders including pain, inflammatory diseases, allergic disorders, CNS disorders, skin disorders, cough and gastrointestinal disorders.

US 6117855 describes the use of a CNS-penetrant NK_1 receptor antagonist and an antidepressant or anti-anxiety for the manufacture of a medicament for the treatment or prevention of depression and/or anxiety.
There is however no specific disclosure of such combinations with paroxetine.

WO 01/25219 and WO 02/32867 teach that the NK_1 receptor antagonists described therein may be administered in combination with a SSRI agent. However, there is no specific teaching concerning the use of a combination of paroxetine with the compounds claimed therein in the treatment of depression and /or anxiety.

We have found that therapeutic compositions comprising a combination of paroxetine and a NK_1 receptor antagonist provide a useful and unexpectedly advantageous combination for the treatment of depression and/or anxiety.

In particular, it has now been found that by combining paroxetine and a NK_1 receptor antagonist, a synergistic anti-depressive and/or anti-anxiety effect is achieved.

Furthermore, the synergistic effect is also observed when each component is employed in the combination in an amount or dosage which is less than that normally expected to produce a fully effective therapeutic response when the component is administered alone.

It is a feature of this invention that the use of such a combination will provide one or more of the following effects: the synergistic effect of the combination providing a more efficacious anti-depressive and/or anti-anxiety drug and/or a better tolerated drug treatment and/or a more rapid onset of the anti-depressive and/or anti-anxiety activity.

When used in any of the contexts or aspects of the present invention, paroxetine may be administered as the free base, or in the form of any physiologically acceptable salt thereof, including all hydrated or anhydrous forms and all polymorphic forms of such salts. In particular, references to paroxetine include, without limitation, paroxetine hydrochloride, paroxetine hydrochloride hemihydrate, paroxetine hydrochloride anhydrate, paroxetine mesylate and all polymorphic forms thereof.

According to one aspect of the invention, there is provided a combination comprising paroxetine and a NK_1 receptor antagonist.

NK_1 receptor antagonists for use in the present invention include those generically and specifically disclosed in the following patent specifications whose disclosures are incorporated by reference:

European Patent Specification Nos. 284942, 327009, 333174, 336230, 360390, 394989, 428434, 429366, 436334, 443132, 446706, 482539, 484719, 499313, 512901, 512902, 514273, 514275, 517589, 520555, 522808, 525360, 528495, 532456, 533280, 577394, 591040, 615751, 684257, 1176144, 1110958, 1176144, 1172106, 1103545, and 1256578; and in

International Patent Specification Nos. 90/05525, 90/05729, 91/02745, 91/12266, 91/18016, 91/18899, 92/01688, 92/06079, 92/15585, 92/17449, 92/20676, 92/21677, 92/22569, 93/00331, 93/01159, 93/01160, 93/01165, 93/01169, 93/01170, 94/01402, 94/26735, 95/06645, 95/08549, 95/14017, 95/16679, 95/18124, 95/23798, 95/28389, 95/33744, 96/05181, 96/18643, 96/21661, 96/29326, 96/32386, 96/34857, 96/37489, 97/02824, 97/05110, 97/08166, 97/13514, 97/14671, 97/16440, 97/17362, 97/19074, 97/19084, 97/19942, 97/21702, 97/22597, 97/22604, 97/23455, 97/24324, 97/24350, 97/25322, 97/25988, 97/27185, 97/30989, 97/30990, 97/30991, 97/32865, 97/38692,

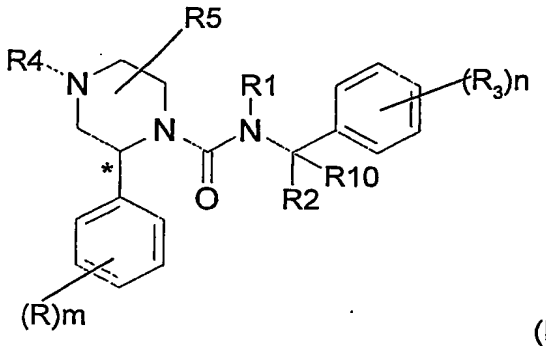
97/44035, 97/49393, 97/49710, 98/02158, 98/04561, 98/07694, 98/07722, 98/08826, 98/13369, 98/17276, 98/18761, 98/18785, 98/18788, 98/20010, 98/24438, 98/24439, 98/24440, 98/24441, 98/24442, 98/24442, 98/24443, 98/24444, 98/24445, 98/24446, 98/24447, 98/28297, 98/43639, 98/45262, 98/49170, 98/54187, 98/57954, 98/57972, 99/00388, 99/01444, 99/01451, 99/07677, 99/07681, 99/09987, 99/21823, 99/24423, 99/25364, 99/26924, 99/27938, 99/36424, 99/52903, 99/59583, 99/59972, 99/62893, 99/62900, 99/64000, 00/02859, 00/06544, 00/06571, 00/06572, 00/06578, 00/06580, 00/15621, 00/20003, 00/21512, 00/21564, 00/23061, 00/23062, 00/23066, 00/23072, 00/20389, 00/25745, 00/26214, 00/26215, 00/34243, 00/34274, 00/39114, 00/47562, 01/77069, 01/25233, 01/30348, 01/87866, 01/94346, 01/90083, 01/87838, 01/85732, 01/77100, 01/77089, 01/77069, 01/46176, 01/46167, 01/44200, 01/32625, 01/29027, 01/25219, 02/32865, 02/00631, 02/81461, 02/92604, 02/38575, 02/57250, 02/22574, 02/74771, 02/26710, 02/28853, 02/102372, 02/85458, 02/81457, 02/74771, 02/62784, 02/60898, 02/60875, 02/51848, 02/51807, 02/42280, 02/34699, 02/32867, 02/32866, 02/26724, 02/24673, 02/24629, 02/18346, 02/16344, 02/16343, 02/16324, 02/12168, 02/08232 and 02/06236; and in

US Patent Specification Nos. 4839465, 5338845, 5594022, 6169097, 6197772, 6222038, 6204265, 6329392, 6316445, 2001039286, 2001034343, 2001029297, 2002193402, 2002147212, 2002147207, 2002143003 and 2002022624; and in

British Patent Specification Nos. 2216529, 2266529, 2268931, 2269170, 2269590, 2271774, 2292144, 2293168, 2293169 and 2302689; and in

Japanese Patent Specification No 6040995.

A particularly useful class of NK1 receptor antagonists for use in the combinations of the present invention is represented by those compounds described in WO 0125219 having the general formula(I)



(I)

wherein

R represents a halogen atom or a C_{1-4} alkyl group;

R_1 represents hydrogen or a C_{1-4} alkyl group;

R_2 represents hydrogen, a C_{1-4} alkyl, C_{2-6} alkenyl or a C_{3-7} cycloalkyl group; or R_1 and R_2 together with nitrogen and carbon atom to which they are attached respectively represent a 5 to 6 membered heterocyclic group;

R_3 represents a trifluoromethyl, a C_{1-4} alkyl, a C_{1-4} alkoxy, a trifluoromethoxy or a halogen group;

R_4 represents hydrogen, a $(CH_2)qR_7$ or a $(CH_2)rCO(CH_2)pR_7$ group;

R_5 represents hydrogen, a C_{1-4} alkyl or a COR_6 group;

R_6 represents hydrogen, hydroxy, amino, methylamino, dimethylamino a 5 membered heteroaryl group containing 1 to 3 heteroatoms selected from oxygen, sulphur and nitrogen or a 6 membered heteroaryl group containing 1 to 3 nitrogen atoms;

R_7 represents hydrogen, hydroxy or NR_8R_9 wherein R_8 and R_9 represent independently hydrogen or C_{1-4} alkyl optionally substituted by hydroxy or by amino;

R_{10} represents hydogen, a C1-4 alkyl group or

R_{10} together with R_2 represents a C_{3-7} cycloalkyl group;

m is zero or an integer from 1 to 3;

n is zero or an integer from 1 to 3;

both p and r are independently zero or an integer from 1 to 4;

q is an integer from 1 to 4;

provided that, when R_1 and R_2 together with nitrogen and carbon atom to which they are attached respectively represent a 5 to 6 membered heterocyclic group:

i) m is 1 or 2;

ii) when m is 1, R is not fluorine and

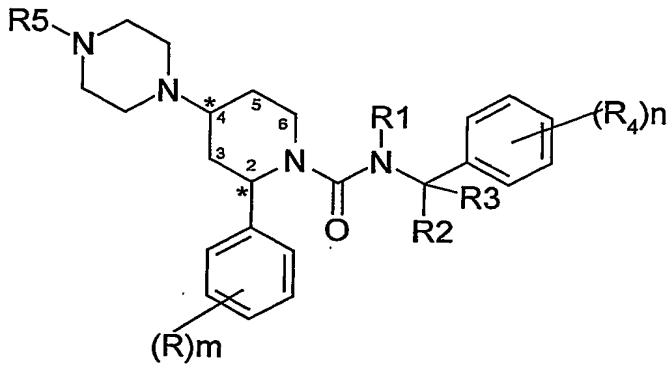
iii) when m is 2, the two substituents R are not both fluorine

and pharmaceutically acceptable salts and solvates thereof.

Within this class, particularly preferred compounds include those wherein R is selected independently from halogen or methyl, R_3 is trifluoromethyl both at the 3 and 5 position, R_1 is hydrogen or methyl, R_2 is hydrogen, methyl, 2-propenyl, or a cyclopropyl group or together with R_1 is a 3,6-dihydro-2H-pyridin-1yl, a piperidin-1-yl or a pyrrolidin 1-yl group, R_{10} represents hydrogen, a methyl or R_{10} together with R_2 is a cyclopropyl group, R_4 is hydrogen, an aminoacetyl or amino ethyl group and R_5 is hydrogen or a methyl group.

A particularly preferred compound of formula (I) for use in the invention is 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide and physiologiaclly acceptable salts thereof (e.g. methansulphonate or hydrochloride).

Further examples of suitable NK1 receptor antagonists for use in the combinations of the present invention include those described in WO 0232867 having the general formula(II)



(II)

wherein

R represents a halogen atom or a C_{1-4} alkyl group;

R_1 represents a C_{1-4} alkyl group;

R_2 represents hydrogen or a C_{1-4} alkyl group;

R_3 represents hydrogen, or a C_{1-4} alkyl group;

R_4 represents a trifluoromethyl group;

R_5 represents hydrogen, a C_{1-4} alkyl group or $C(O)R_6$;

R_6 represents C_{1-4} alkyl, C_{3-7} cycloalkyl, $NH(C_{1-4}$ alkyl) or $N(C1\text{-}4alkyl)_2$;

m is zero or an integer from 1 to 3;

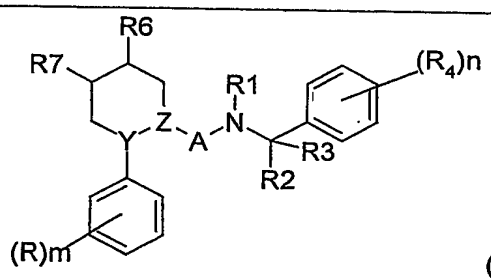
n is an integer from 1 to 3;

and pharmaceutically acceptable salts and solvates thereof.

A particularly preferred compound of formula (II) for use in the combinations of the invention is

4-(S)-(4-Acetyl-piperazin-1-yl)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid, [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide and pharmaceutically acceptable salts (e.g. hydrochloride, methanesulphonate, sulphate, p-toluensulphonate) or solvates thereof.

Another further preferred class of Nk1 receptor antagonists for use in the present invention is that described in PCT /EP03/01308 having general formula(III)



(III)

wherein

R represents halogen or C_{1-4} alkyl ;

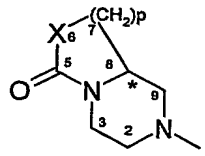
R_1 represents C_{1-4} alkyl;

R_2 or R_3 independently represent hydrogen or C_{1-4} alkyl;

R_4 represents trifluoromethyl, C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethoxy or halogen;

R_5 represents hydrogen, C_{1-4} alkyl or C_{3-7} cycloalkyl;

R_6 is hydrogen and R_7 is a radical of formula (W):



(W)

or R_6 is a radical of formula (W) and R_7 is hydrogen;

X represents CH_2, NR_5 or O;

Y represents Nitrogen and Z is CH or Y represents CH and Z is Nitrogen;

A represents C(O) or S(O)q, provided that when Y is nitrogen and Z is CH, A is not S(O)q;

m is zero or an integer from 1 to 3;

n is an integer from 1 to 3;

p and q are independently an integer from 1 to 2;

and pharmaceutically acceptable salts and solvates thereof.

Particularly preferred compounds of formula (III) include those in which R_6 is hydrogen, R_7 is a radical of formula (W) and Y is CH and Z is nitrogen or wherein R_6 is a radical of formula (W), R_7 is a hydrogen and Y is nitrogen and Z is CH; A is C(O) and X is CH_2.

A particularly preferred compound of formula (III) for use in the invention is 2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aS)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide and pharmaceutically acceptable salts (e.g. hydrochloride, methanesulphonate or maleate) and solvates thereof.

The subject matter of the above identified patent applications is incorporated herein by reference.

A preferred embodiment of the invention provides a combination ofparoxetine and a NK1 receptor antagonist selected from
2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide and physiologically acceptable salts thereof (e.g. methansulphonate and hydrochloride);
2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aS)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide and physiologically acceptable salts thereof (e.g. hydrochloride, methanesulphonate or maleate) ;
2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aS)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide and physiologically acceptable salts thereof (e.g. hydrochloride, methanesulphonate or maleate);
2-methoxy-5-(5-trifluoromethyl-tetrazol-1-yl-benzyl)]-(2S-phenyl-piperidin-3S-yl)-amine.

A particularly preferred combination according to the invention comprises paroxetine and 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide methansulphonate.

A further particularly preferred combination according to the invention comprises paroxetine hydrochloride and 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide methansulphonate.

A further particularly preferred combination according to the invention comprises paroxetine hydrochloride hemihydrate and 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide methansulphonate.

A further particularly preferred combination according to the invention comprises paroxetine hydrochloride anhydrate and 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide methansulphonate.

A further particularly preferred combination according to the invention comprises paroxetine mesylate and 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide methansulphonate.

The present invention thus provides a method for the treatment of depression and/or anxiety in a mammal including a human, which comprises treating said animal with a therapeutically effective amount of a combination of paroxetine and a NK1 receptor antagonists.

A preferred embodiment of the invention provides a method for the treatment of depression and/or anxiety in a mammal including a human, which comprises treating said animal with a therapeutically effective amount of a combination ofparoxetine and a NK1 receptor antagonists selected from

2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide and pharmaceutically acceptable salts thereof (e.g. methansulphonate and hydrochloride);

2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aS)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide pharmaceutically acceptable salts (e.g. hydrochloride, methanesulphonate or maleate) ;

2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aS)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide pharmaceutically acceptable salts (e.g. hydrochloride, methanesulphonate or maleate);

2-methoxy-5-(5-trifluoromethyl-tetrazol-1-yl-benzyl)]-(2S-phenyl-piperidin-3S-yl)-amine).

More particularly, the present invention provides a method for the treatment of depression and/or anxiety in a mammal including a human, which comprises treating said mammal with a therapeutically effective amount of a combination ofparoxetine and 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide and physiologically acceptable salts thereof (e.g. methansulphonate and hydrochloride).

In a further preferred aspect, the present invention provides a method for the treatment of depression and/or anxiety in a mammal including a human, which comprises treating said mammal with a therapeutically effective amount of a combination ofparoxetine and 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide methansulphonate.

In a further preferred aspect, the present invention provides a method for the treatment of depression and/or anxiety in a mammal including a human, which comprises treating said mammal with a therapeutically effective amount of a combination of paroxetine hydrochloride and 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide methansulphonate.

In a further preferred aspect, the present invention provides a method for the treatment of depression and/or anxiety in a mammal including a human, which comprises treating said mammal with a therapeutically effective amount of a combination of paroxetine hydrochloride hemihydrate and 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide methansulphonate.

In a further preferred aspect, the present invention provides a method for the treatment of depression and/or anxiety in a mammal including a human, which comprises treating said mammal with a therapeutically effective amount of a combination of paroxetine hydrochloride anhydrate and 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide methansulphonate.

In a further preferred aspect, the present invention provides a method for the treatment of depression and/or anxiety in a mammal including a human, which comprises treating said mammal with a therapeutically effective amount of a combination ofparoxetine mesylate and 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide methansulphonate.

Reference herein to treatment extends to prophylaxis as well as the treatment of established depression and/or anxiety or symptoms.

As used herein, the term depression includes depressive disorders. Thus, for example, depressive disorders include Major Depressive Disorders (MDD), including bipolar depression, unipolar depression, single or recurrent major depressive episodes, recurrent brief depression, with or without psychotic features, catatonic features, melancholic features including anorexia, weight loss, atypical features, anxious depression, cyclothymic or postpartum onset.

Other mood disorders encompassed within the term major depressive disorders include dysthymic disorders with early or late onset and with or without atypical features, neurotic depression, post-traumatic stress disorders and social phobia; dementia of the Alzheimer's type, with early or late onset, with depressed mood; vascular dementia with depressed mood; mood disorders induced by alcohol, amphetamines, cocaine, hallucinogens, inhalants, opioids, phencyclidine, sedatives, hypnotics, anxiolytics and other substances; schizoaffective disorder of the depressed type; and adjustment disorder with depressed mood. Major depressive disorders may also result from a general medical condition including, but not limited to, myocardial infarction, diabetes, miscarriage or abortion, etc.

As used herein, the term anxiety includes anxiety disorders, such as panic disorders with or without agoraphobia, agoraphobia, phobias, for example, social phobias or agoraphobia, obsessive-compulsive disorder, stress disorders including post-traumatic stress disorders, generalised anxiety disorders, acute stress disorders and mixed anxiety-depression disorders

The advantageous profile of anti-anxiety activity obtained by the administration of paroxetine with an NK1 receptor antagonist can be demostrated in the gerbil social interaction model, according to the method described by Cheeta et al. (Cheeta S. et al., 2001. Brain Research 915: 170-175).

It will be appreciated that the compounds of the combination may be administered simultaneously, either in the same or different pharmaceutical formulations or sequentially. If there is sequential administration, the delay in administering the second and any subsequent active ingredient should not be such as to lose the benefit of a synergistic therapeutic effect of the combination of the active ingredients. It will also be

understood that the compounds of the combination or the physiologically functional derivatives of any thereof, whether presented simultaneously or sequentially, may be administered individually or in multiples or in any combination thereof.

In a further aspect of the present invention is provided the use of paroxetine and an NK1 receptor antagonist in the manufacture of a medicament for simultaneous or sequential administration for the treatment and/or prophylaxis of depression and/or anxiety, wherein the Nk1 receptor antagonist is selected from
2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide and physiologically acceptable salts thereof (e.g. methansulphonate and hydrochloride);
2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aS)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide and physiologically acceptable salts (e.g. hydrochloride, methanesulphonate or maleate);
2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aS)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide and physiologically acceptable salts (e.g. hydrochloride, methanesulphonate or maleate);
2-methoxy-5-(5-trifluoromethyl-tetrazol-1-yl-benzyl)]-(2S-phenyl-piperidin-3S-yl)-amine).

In a more preferred embodiment, the present invention provides the use of paroxetine and an NK1 receptor antagonist in the manufacture of a medicament for simultaneous or sequential administration wherein the NK1 receptor antagonist is 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide or a physiologically acceptable salt thereof (e.g. methansulphonate or hydrochloride).

In a further preferred embodiment, the present invention provides the use of paroxetine and 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide or a physiologically acceptable acceptable salt thereof (e.g. methanesulphonate or hydrochloride) in the manufacture of a medicament for simultaneous or sequential administration for the treatment and/or prophylaxis of depression and/or anxiety.

In a further preferred embodiment, the present invention provides the use of paroxetine and 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide methanesulphonate in the manufacture of a

medicament for simultaneous or sequential administration for the treatment and/or prophylaxis of depression and/or anxiety.

In a further preferred embodiment, the present invention provides the use of paroxetine hydrochloride and 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide methanesulphonate in the manufacture of a medicament for simultaneous or sequential administration for the treatment and/or prophylaxis of depression and/or anxiety.

In a further preferred embodiment, the present invention provides the use of paroxetine hydrochloride hemihydrate and 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide methanesulphonate in the manufacture of a medicament for simultaneous or sequential administration for the treatment and/or prophylaxis of depression and/or anxiety.

In a further preferred embodiment, the present invention provides the use of paroxetine hydrochloride anhydrate and 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide methanesulphonate in the manufacture of a medicament for simultaneous or sequential administration for the treatment and/or prophylaxis of depression and/or anxiety.

In a further preferred embodiment, the present invention provides the use of paroxetine mesylate and 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide methanesulphonate in the manufacture of a medicament for simultaneous or sequential administration for the treatment and/or prophylaxis of depression and/or anxiety.

The synergistic effects of the combination ofparotexine and the Nk1 receptor antagonist n may be seen over a wide range of ratios of combination of the components, for example, from 1: 100 to 100: 1 (by weight), such as 1:50 to 50:1 (by weight).

Each of the components of the combination ofparotexine and the Nk1-receptor antagonist may thus be employed in a dosage which is therapeutically effective when that component is administered alone. However, in a preferred aspect of the invention, each component may be employed in the combination in a dosage which is less than that

normally expected to produce a fully effective therapeutic response when the component is administered alone.

The amount of a combination of paroxetine and NK1 receptor antagonist required to be effective as an antidepressive and/or anti-anxiety may, of course, vary and is ultimately at the discretion of the medical practitioner. The factors to be considered include the route of administration and nature of the formulation, the subject mammal's body weight, age and general condition and the nature and severity of the condition to be treated.

In general, a suitable dose of paroxetine for administration to a human for the treatment of depression and/or anxiety as a single therapy may be in a dose of 20 or 400 mg per day, Paroxetine is advantageously administered by oral route once a day.

According to the present invention a suitable dose of paroxetine for administration in combination with a Nk1 receptor antagonist to a human for the treatment of depression and/or anxiety may be within the single therapy effective dose range. In a preferred aspect of the invention, the dose of paroxetine administered in combination with an NK1 antagonist may surprisingly be lower than the single therapy dose, in particular from 1 to 20mg per day, preferably from 1 to 10mg per day, and more preferably from 2.5 to 10mg per day..

In general, a suitable dose of NK1 receptor antagonist for administration to a human as a single therapy may be in the range of 1 to 300 mg per day, depending upon the particular compound.

According to the present invention, a suitable dose of an NK1 receptor antagonist for administration in combination with paroxetine maybe within this singe therapy effective dose range. In a preferred aspect of the invention, the dose of the NK1 receptor antagonist administered in combination with paroxetine may surprisingly be lower than the normal single therapy dose, in particular from 1 to 25 mg per day, preferably from 1 to 10 mg per day and more preferably from 1 to 7.5 mg per day.

Combinations according to the invention in which the dosage of the individual paroxetine and NK1 receptor antagonist components are administered below the usual single therapeutic dosages show surprising and synergistic levels of efficacy for the treatment and/or prophylaxis of depression and/or anxiety.

Unless otherwise indicated, all weights of active ingredients are calculated in terms of the drug *per se*. The desired dose may preferably be presented as one, two, three, four, five, six or more sub-doses administered at appropriate intervals throughout the day.

The components of the combination which may be referred to as active ingredients may be administered for therapy to an animal e.g. a mammal including a human in a conventional manner.

While it is possible for the active ingredients of the combination to be administered as the raw chemical, it is preferable to present them as a pharmaceutical formulation. Pharmaceutical formulations according to the present invention comprise a combination according to the invention together with one or more pharmaceutically acceptable carriers or excipients and optionally other therapeutic agents. The carrier(s) must be acceptable in the sense of being compatible with the other ingredients of the formula and not deleterious to the recipient thereof. When the individual components of the combination are administered separately, they are generally each presented as a pharmaceutical formulation. The references hereinafter to formulations refer, unless otherwise stated, to formulations containing either the combination or a component thereof.

A combination of paroxetine and a Nk1 receptor antagonist may conveniently be presented as a pharmaceutical formulation in a unitary dosage form.

Pharmaceutical formulations are often prescribed to the patient in "patient packs" containing the whole course of treatment in a single package, usually a blister pack. Patient packs have an advantage over traditional prescriptions, where a pharmacist divides a patient's supply of a pharmaceutical from a bulk supply, in that the patient always has access to the package insert contained in the patient pack, normally missing in traditional prescriptions. The inclusion of a package insert has been shown to improve patient compliance with the physician's instructions and, therefore, lead generally to more successful treatment.

It will be understood that the administration of the combination of the invention by means of a single patient pack, or patient packs of each formulation, containing within a package insert instructing the patient to the correct use of the invention is a desirable additional feature of this invention.

According to a further aspect of the invention provided is a multiple, for example, double or triple, pack comprising at least paroxetine and a Nk1 receptor antagonist and an information insert containing directions on the use of the combination of the invention.

Formulations include those suitable for oral, rectal, nasal, topical (including transdermal, buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. Such methods represent a further feature of the present invention and include the step of bringing into association the active ingredients with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, caplets, cachets or tablets each containing a predetermined amount of the active ingredients; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredients in a free-flowing form such as a powder or granules, optionally mixed with a binder (e.g. povidone, gelatin, hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (e.g. sodium starch glycollate, sodium croscarmellose cross-linked povidone, cross-linked sodium carboxymethyl cellulose) surface-active or dispersing agent. Molded tablets may be made by molding a mixture of the powdered compound moistened with an inert liquid diluent in a suitable machine. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredients therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredients in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier. Formulations for rectal administration may be presented as a suppository with a suitable base comprising, for example, cocoa butter or polyethylene glycols.

Topical administration may also be by means of a transdermal iontophoretic device.

Formulations suitable for vaginal administration may be presented as tablets, pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Pharmaceutical formulations suitable for rectal administration wherein the carrier is a solid are most preferably presented as unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by admixture of the active combination with the softened or melted carrier(s) followed by chilling and shaping in molds.

Formulations suitable for parenteral administration include aqueous and nonaqueous isotonic sterile injection solutions which may contain anti-oxidants, buffers, preservatives and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents; and liposomes or other microparticulate systems which are designed to target the compound to blood components or one or more organs. The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example, those suitable for oral administration may include such further agents as sweeteners, thickeners and flavoring agents.

The pharmaceutical composition of the invention containing the two active ingredients may be prepared according to conventional techniques well known in the pharmaceutical industry. Thus, for example the paroxetine and the NK1 receptor anatgonists may be admixed together with suitable excipients such as those described above for the formulation of each of the active ingredients separately. Tablets may be prepared, for example by direct compression of such a mixture or using other conventional methods. Bilayer tablets may be prepared according to conventional procedure. Thus, for example, by separately compressing the two blends in a suitable tabletting machine with two filling stations. Capsules may be prepared by filling the blend along with suitable excipients into gelatin capsules, using a suitable filling machine. Controlled release forms for oral or rectal administration may be formulated in a conventional manner associated with controlled release forms.

Biological data:

The advantageous profile of anti anti-anxiety activity obtained by the administration of paroxetine with an NK1 receptor antagonist can be demostrated in the gerbil social interaction model.

In the experiment 1 the NK1 receptor antagonist used is 2-methoxy-5-(5-trifluoromethyl-tetrazol-1-yl-benzyl)]-(2S-phenyl-piperidin-3S-yl)-amine(herein after compound A)

In the experiment 2 the NK1 receptor antagonist used is 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide methansulphonate (herein after compound B)

Experiment 1

Paroxetine (0.3 mg/kg p.o.), compound A (0.03 mg/kg i.p.) and a combination of paroxetine (0.3 mg/kg p.o.) and compound A (0.03 mg/kg i.p.) were administered in mongolian gerbils to assess the effect on time spent in active social interactions.

Experiment 2

Paroxetine (0.3 mg/kg p.o.), compound B (0.1 mg/kg i.p) and a combination of paroxetine (0.3 mg/kg p.o.) and compound B (0.1 mg/kg i.p.) were administered..

The results obtained one hour after administration, express as a percentage variation of the time spent in active social interaction by each animal, in respect to the value obtained by treatment of control animals are summarised below.

	Compound		
	paroxetine 0.3mg/kg	**Compound A 0.03mg/kg**	**paroxetine/0.3mg/kg GR205171 0.03mg/kg**
% variation	**- 2%**	**+ 19.9%**	**+ 40.3%**

	Compound		
	paroxetine 0.3mg/kg	**Compound B 0.1mg/kg**	**paroxetine/0.3mg/kg GW597599 0.1mg/kg**
% variation	**- 2%**	**- 8%**	**+ 56%**

The variation of amount of time spent in active social interaction by each animal after treatment of a combination of paroxetine and compound A or paroxetine and compound B is significantly greater than was to be expected from a consideration of the therapeutic response of the components administered separately.

Thus, the above results provide evidence for a synergistic effect between an NK1 receptor antagonist with paroxetine in a social stress assay.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation, the following claims:

CLAIMS

1. A composition comprising paroxetine and a Nk1 receptor antagonist.

2 A composition as claimed in claim 1 wherein the Nk1 receptor antagonist is elected from

2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide ;

2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aS)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide;

2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aS)-6-oxo-hexahydro-pyrrolo[1,2-*a*]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide

2-methoxy-5-(5-trifluoromethyl-tetrazol-1-yl-benzyl)]-(2S-phenyl-piperidin-3S-yl)-amine; and physiologically acceptable salts thereof.

3 A composition according to claim 1 wherein the Nk1 receptor antagonist is 2-(S)-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide methansulphonate.

4 A composition according to any of claims 1 to 3 for use in the treatment and or prophylaxis of depression and /or anxiety.

5 A method for the treatment and/or prophylaxis of depression and/or anxiety in a mammal including a human, which comprises treating said animal with a therapeutically effective amount of a composition as claimed in any of claims 1 to 3.

6 A method according to any of the claims 1 to 3 wherein the composition is administered as a single combined formulation.

7. A pharmaceutical formulation comprising a composition according to any of the claims 1 to 3 together with one or more pharmaceutically acceptable carriers or excipients.

8. The use of paroxetine and an NK1 receptor antagonist in the manufacture of a medicament for simultaneous or sequential administration for the treatment and/or prophylaxis of depression and /or anxiety.

ABSTRACT

The present invention relates to therapeutic combinations comprising paroxetine and a Nk1 receptor antagonist, to pharmaceutical compositions containing said combinations and their use in the treatment of depression and /or anxiety

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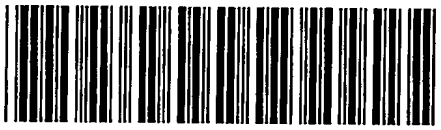

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